

Applicants' Response

Applicants respond below to each section of recent Examination by including (1) a restatement of the rejection/objection in single spaced type, followed by (2) Applicant's response in double space type.

Claim Rejections - 35 USC § 112

Claim 38 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the "invention. Specifically, the Examiner indicated that Claim 38 does not recite a positive method step, and therefore is not further limiting.

Applicants have amended Claim 38 to cite a positive method step by indicating the change in the concentration of the analyte of a patient has occurred, as a condition precedent, after an ischemic stroke or viral infection, or having received insulin, an illegal drug, a biological toxin, or a biological warfare agent as a step preceding those given in Claim 1.

Claim 38 now cites a change in concentration of the analyte has occurred after one of two events, or having received one of the four listed agents. In view of the submitted amendments, Applicants respectfully request the present rejection of Claim 38 under 35 USC § 112, second paragraph, be removed.

Claim Rejections - 35 USC § 101

Claims 11 - 21 were rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, Claim 11 was indicated to recite "additionally at least one of said light emitter or said light detector is also implanted in the body" which improperly included a portion of a living being ("the body") as part of the claimed structure. The Examiner indicated the claim should recite "... is also adapted to be implanted ..." to avoid including the body as part of the claimed subject matter. In addition, claim 18 also must be similarly amended to avoid including the body as part of the claimed subject matter.

Applicants have amended Claims 11 and 18 as recommended by the Examiner to indicate the device has been adapted to be implanted. Applicants appreciate and thank the Examiner for his recommendations. Applicants submit that the amended claim no longer reads on including a portion of the living being ("the

("the body"). In view of the submitted amendments to Claims 11 and 18, Applicants respectfully request the present rejection of claims 11-21 under 35 USC § 101 be removed.

Claim Rejections - 35 USC § 103

Claims 1 - 8, 10, 11, 13 - 16, 19 - 21, and 33 - 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al. in view of Van Antwerp et al. Chick et al. teach a method and arrangement for detecting an analyte in the human body comprising placing an analyte detector with two fluorescent dyes within the body, illuminating the detector, and measuring the analyte concentration based upon the ratio of energy emitted by the two dyes as a result of fluorescent resonant energy transfer (FRET) between them (col. 2, line 31 - col. 6, line 44). Further, a drug delivery system in communication with the analyte detector may be implanted in the body such that a feedback loop is established wherein a prescribed amount of drug is released when the measured analyte concentration exceeds a certain threshold (col. 6, lines 1-5). The illuminating energy is visible light at a wavelength of 472 nm (col. 11, lines 36-47) and the analyte measured may be a protein in the blood (the level of which may vary under certain physiological states) or an antigen or a narcotic such as cocaine or heroin (col. 5, lines 15-50). Chick et al. teaches an implantable sensor with transdermal determination of analyte concentrations (column 6, lines 6 - 34; column 16, line 23 - column 17, line 32). Van Antwerp et al. (Figure 6 and the description thereof) teach an alternate arrangement that includes completely implantable emitter, detector, and sensing elements. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the combination to use a completely implantable arrangement, as taught by Van Antwerp et al., since this is merely an alternate equivalent expedient.

It is noted that Applicant's remarks, page 10, are relevant to the above recited combination. In essence, Applicant alleges that the combination fails because Van Antwerp et al. is not a FRET-based system, and therefore cannot suggest the desirability of a completely implanted FRET-based system. However, this is not persuasive, as the teaching of Van Antwerp et al. discloses that a totally implanted optical measurement system is an alternative to an implanted system and possesses certain advantages. One of ordinary skill in the art would recognize that these advantages are equally relevant to problems one would identify in a FRET-based measurement arrangement. Contrary to Applicant's assertions, the teaching of Van Antwerp et al. is relevant to the problems one would encounter with the system of Chick et al. and teaches a solution that would be within the skill in the art to implement therewith.

Applicants respectively traverse the present rejections. Although, Chick et al. teaches a FRET detector system, and Van Antwerp et al. teaches an arrangement that includes an implantable emitter, detector, and sensing elements, these are insufficient to render obvious claimed invention as now amended.

Applicants have amended their claims to specifically incorporate features of Claim 9 into Claim 1. Claim 1 now directly specifies a troponin antibody based FRET detection system, which is as specifically taught and supported in the specification.

specification. The Examiner has indicated in his rejection of Claim 9 that Chick et al. and Van Antwerp does not teach a troponin based detection system. In view of the Examiner's own conclusion that the Chick et al. and Van Antwerp et al. does not teach a troponin based detection system, Applicants respectively request the present rejection be removed and they will then turn to the rejections made to Claim 9 (now incorporated in part into Claims 1-8, 10-11, 13-16, 19-21, and 33-38).

5. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al. and Van Antwerp et al. as applied to Claim 1 above, and further in view of Wicks et al. and Khaw et al. Chick et al. in view of Van Antwerp et al. teach all of the features of the invention except that the sensed protein is troponin-T antigen. Wicks et al. teach that troponin I is a protein that is a marker for cardiac damage (column 1, lines 24 - 41). It would have been obvious to one of ordinary skill in the art at the time of the invention to implement Chick et al. with sensitivity for troponin, since Chick et al. teach that their method and arrangement are suitable for detecting proteins in the blood that are indicative of physiological states (column 9, line 59 - column 12) and Wicks et al. teach that troponin I is a blood protein that is a marker for cardiac damage. Further, Khaw et al. teach that troponin I and T are alternate equivalents for sensing heart attack related events (paragraphs [0002] and [0011]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the combination to sense troponin T, since Khaw et al. teach that this is an alternate equivalent expedient to troponin I and it has generally been held to be within the skill level of the art to substitute alternate equivalent expedients.

Applicants traverse the current rejection in view of the submitted amendments to Claim 1 incorporating specific features of Claim 9.

Chick et al. was cited for teaching a FRET detector system wherein an antigen is used to detect a protein, and Van Antwerp et al. Wicks et al was cited to suggest that troponin T is a useful cardiac marker, and Khaw teaches that troponin I and troponin T are alternate equivalents as protein markers for cardiac change.

First, Applicants wish to indicate that the fact that Chick teaches a FRET detection system wherein an antigen is used to detect a protein, does not lead to the conclusion that one skilled in the art can modify any antigen with a FRET detector and that it still will be useful. One skilled in the art would not be able to reasonably predict whether after modification of the antibody with the FRET detector that the antibody would still bind the antigen. Further, because the FRET distances between the two detectors and their position is critical for the system to be operable, one skilled in the art would not understand whether such a system could be created for cardiac troponin at the time of the invention. The answer to that question would turn on actual experimentation as shown by the Applicants.

Second, the fact that Wicks teaches troponin T is a useful cardiac marker, and Khaw teaches that troponin 1 and troponin T are alternate equivalents as protein markers for cardiac change, does not mean they are chemically equivalent and that they will behave in the same way as proteins when modified. Further, nowhere in any of the cited references is there a teaching or suggestion that one can make an analyte FRET detector using a troponin antibody that acts as the analyte FRET detector. Behavior of proteins, including antibodies, is generally understood to be unpredictable after modification, including attachment of a FRET detection system. Whether the antibodies will continue to work after FRET modification would turn in part on whether the antibodies still bind the antigen after attaching of the FRETs and whether the first FRET in relation to the second FRET is sufficient for measured energy transfer is based upon reading of Applicants specification. The Examiner's arguments boils down to an argument that it would be obvious to try the purposed system with the hindsight of Applications specification and examples showing that it would in fact work.

In view of the amendments to the claims and arguments presented above, Applicants respectfully request the present rejection to claim 9 be removed and as applied to Claims 1-8, 11, 13-16, 19-21, and 33-38.

6. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al. and Van Antwerp et al. as applied to claim 11 above, and further in view of Kwon. The combination teaches all of the features of the claimed invention except for the particularly claimed fluorescent dyes. Kwon teaches monitoring analyte concentrations in the body using FRET, wherein one of the dyes which may be used is tetramethylrhodamine isothiocyanate. It would have been obvious to one having ordinary skill in the art at the time the invention was made to use with the FRET system disclosed by the combination with the fluorescent dye tetramethylrhodamine isothiocyanate, since Kwon teaches that this dye allows for effective FRET analyte concentration measurements.

As previously indicated in Applicant's previous discussion of Claim 9, the fact that Chick et al. teaches a FRET detector system, and Van Antwerp et al. teaches an arrangement that includes an implantable emitter, detector, and sensing elements, and Wicks suggests that troponin 1 is a useful cardiac marker, and that Kwon teaches analyte concentrations in the body can be determined by FRET technology, does not lead to a reasonable expectation, teaching, or suggestion that one can

one can make an antibody based FRET detector system for cardiac troponin.

In view of Applicants submitted amendments to the claims indicating specifically the invention is directed to an antibody detector for cardiac troponin which contains at least one of the FRET detectors, and this distinction is neither taught or suggested by Chick et al., Van Antwerp et al., Wicks et al., Kwon, or Khaw individually or collectively, Applicants, respectfully request the present rejection of Claim 11 over these references be removed.

Claim 17 is rejected under 35 USC § 103(a) as being unpatentable over Chick et al. and Van Antwerp et al. as applied to claim 11 (sic.; **Applicants have taken this to be Claim 1**) above, and further in view of Rao et al. (previously cited). The Examiner argues that the combination of references teaches all of the features of the claimed invention except that there is an alert module. Rao et al. teach an alternate FRET system that includes an alert module notify a subject of changes in concentration (see Figure 9 and the description thereof). Therefore the Examiner argues it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the combination to include an alert module, as taught by Rao et al., since this allows a subject to be notified of changing concentrations.

Although, Chick et al. teaches a FRET detector system, Van Antwerp et al. teaches an arrangement that includes an implantable emitter, detector, and sensing elements, and Rao teaches an alternate FRET system that includes an alert module, these are insufficient to render obvious Applicants claimed invention as now amended.

Applicants have previously discussed the arguments as to why Chick et al. and Van Antwerp et al. are insufficient to show the present invention is obvious. The addition of Rao that teaches an alert module does not help overcome the problem that the previous references do not teach or suggest that one skilled in the art could reasonably predict whether a cardiac troponin antibody would operably function in a FRET based detection system. Knowing that the system can have an alert module to notify the subject adds nothing to fill the missing requirements for a clear teaching without experimentation that one could appropriately assemble a working antibody FRET system for cardiac troponin.

In view of Applicants claims that specifically recite that the FRET detector is based on an antibody having at least one of the two fluorescent dyes, and that the antibody still is capable to bind the cardiac troponin antigen, and that the system

operably transfers energy, and this distinction is neither taught or suggested by Chick et al., and Van Antwerp, in view of Rao et al, individually or collectively, Applicants, respectfully request the present rejection of Claim 17 over Chick et al. and Wicks et al. in view of Rao be removed.

Claim 39 was rejected under 35 USC § 103(a) as being unpatentable over Chick et al. and Van Antwerp et al. as applied to claim 1 above, and further in view of Wicks et al. Chick et al was cited for teaching all the features of the invention except that the sensed protein is troponin. However, the Examiner cited Wickes et al. for teaching that troponin I is a protein that is a marker for cardiac damage (column 1, lines 24-41). The Examiner therefore concludes it would have been obvious to one of ordinary skill in the art at the time of the invention to implement Chick et al. with sensitivity for troponin, since Chick et al teach that their method and arrangement are suitable for detecting proteins in the blood that are indicative of physiological states and Wicks et al. teach that troponin I is a blood protein that is a marker for cardiac damage.

Applicants traverse the current rejection in view of the submitted amendments to Claim 1 incorporating specific features of Claim 39.

Although, Chick et al. teaches a FRET detector system, and Van Antwerp et al. teaches an arrangement that includes an implantable emitter, detector, and sensing elements, and Wicks suggests that troponin 1 is a protein marker for cardiac change, no where in either reference, or in combination, is there a teaching or suggestion that one can make a FRET antibody detector for cardiac troponin.

As Applicants have previously indicated, Chick teaches a FRET detection system wherein an antigen is used to detect a protein, does not lead to the conclusion that one skilled in the art can modify any antigen with a FRET detector and that it still will be useful. One skilled in the art would not be able to reasonably predict whether after modification of the antibody with the FRET detector that the antibody would still bind the antigen. Further, because the FRET distances between the two detectors and their position is critical for the system to be operable, one skilled in the art would not understand whether such a system could be created for cardiac troponin at the time of the invention. The answer to that question would turn on actual experimentation as shown by the Applicants.

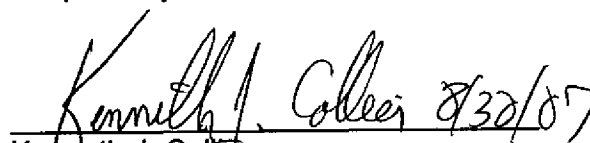
Second, the fact that Wicks teaches troponin T is a useful cardiac marker, and Khaw teaches that troponin 1 and troponin T are alternate equivalents as protein markers for cardiac change, does not mean they are chemically equivalent and that they will behave in the same way as proteins when modified. Further, nowhere in any of the cited references is there a teaching or suggestion that one can make an analyte FRET detector using a troponin antibody that acts as the analyte FRET detector. Behavior of proteins, including antibodies, is generally understood to be unpredictable after modification, including attachment of a FRET detection system. Whether the antibodies will continue to work after FRET modification would turn in part on whether the antibodies still bind the antigen after attaching of the FRETs and whether the first FRET in relation to the second FRET is sufficient for measured energy transfer is based upon reading of Applicants specification. The Examiner's arguments boils down to an argument that it would be obvious to try the purposed system with the hindsight of Applications specification and examples showing that it would in fact work.

Based upon Applicants arguments and amendments repeated here, and submitted in the prior rejections, Applicants respectfully request the present rejection to Claim 39 over these references be removed.

Conclusion

Applicants indicate they believe they have addressed all the issues raised by the Examiner, and respectfully request that the invention as now claimed be allowed to issue.

Respectfully submitted,



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